REMARKS

I. Claim Amendments

Claims 41, 69, 71, and 72 have been canceled.

In claims 2, 5, and 28, the term "Env" has been reintroduced. Support for this amendment is found in the specification at page 12, line 36 to page 13; line 1, page 14, lines 12-13, and page 19, lines 7-8. Applicants note that the term "Env" was previously deleted to overcome the anticipation rejection based on Yu et al. which discloses a Sendai virus vector encoding gp120 that is a part of immunodeficiency viral protein Env. Pending claims 2, 5, and 28 do not recite the phrase "a part of," and therefore do not encompass gp120 as an immunodeficiency viral protein encoded by the vector. Accordingly, the term "Env" has been reintroduced.

In claims 2, 5, and 17, the term "Tat" has been added. Support for this amendment is found in the specification, for example, at page 13, lines 3-4.

In claims 12, 16, and 28, the term "Gag" has been added to cover the broadest scope. Support for this amendment is found in the specification, for example, at page 12, line 36 to page 13, line 4, and page 14, lines 9-13. In claims 12, 28, and 33, the phrase "Rev, Vpu, Vpx, Vpr, Vif, Nef" has been deleted. In view of these amendments, claim 17 has been rewritten to depend from claim 16; and claim 73 has been added.

In claims 33 and 42, the phrase "and a part of any of them" has been deleted.

In claims 67, 68, and 70, the phrase "is a processed product or" has been deleted

and the term "comprises" has been inserted. Support is found in the specification, for example, at page 22, line 33 through page 23, line 7.

Claims 73-79 have been added. Support for claim 73 is found in the specification, for example, at page 13, lines 2-3 and page 22, lines 1-6. Support for claims 74-79 is found in the specification, for example, at page 22, lines 2-14.

No new matter has been added by any of the aforementioned amendments. Applicants reserve the right to pursue any cancelled subject matter in this or a continuing application.

II. New Matter Rejection and Rejection under 35 U.S.C. §112, second paragraph

Claims 67-71 were rejected under 35 U.S.C. §112 on the ground that the phrase "the part is a processed product" is considered to be new matter. Claims 67-71 are also rejected under 35 U.S.C. §112, second paragraph. To expedite prosecution, claims 67-71 have been amended and new claims 74-79 have been added. In view of the present amendment, each of these rejections should be withdrawn.

III. Rejections under 35 U.S.C. §112, first paragraph

Claims 20, 24, 26, 28, 30-33, 37, 39, 41, 43-45, and 63-72 were rejected on the grounds that Applicants' specification does not reasonably enable achieving a vaccine effect by intranasally administering a Sendai viral vector expressing tat, rev, vpu, vpx,

vpr, vif, nef protein, and any parts of an immunodeficiency virus protein. Applicants respectfully disagree.

At the outset, Applicants note that although claims 65 and 66 have been rejected on enablement grounds, claims 2 and 16 from which claims 65 and 66 respectively ultimately depend are free of the enablement rejection. Accordingly, claims 65 and 66 are also free from the enablement rejection, and the rejection of these claims should therefore be withdrawn.

Similarly, claims 67 and 68, which depend from claims which are free of the enablement rejection, are also enabled by the present specification. The rejection as applied to these claims should also therefore be withdrawn.

In addition, the Office maintains that, in light of the specification, "the sole purpose of 'inducing an immune response specific to a virus protein of an immunodeficiency virus in an animal is to reduce HIV/SIV virus replication [Office Action, page 5]." Applicants respectfully disagree.

Independent claims 20 reads:

> 20. (previously presented) A method for inducing an immune response specific to a virus protein of an immunodeficiency virus in an animal, the method comprising the step of intranasally administering to said animal a recombinant Sendai virus gene-transfer vector encoding the immunodeficiency viral protein, wherein the immunodeficiency viral protein comprises a protein selected from the group consisting of Gag, Pol, Env, gp41, Tat, Rev, Vpu, Vpx, Vpr, Vif, Nef, Gag-Pol fusion protein, and a part of any of them.

With respect to claim 20, Applicants note that the specification describes that

results obtained by the instant invention suggest availability of SeV vector for assessment of the cellular immune responses (see page 3, lines 28-30). Thus, reduction of HIV/SIV virus replication is not the sole purpose of "inducing an immune response specific to a virus protein of an immunodeficiency virus in an animal."

Furthermore, referring back to the Office Action dated January 26, 2005, the Examiner asserted that, with respect to the claim breadth, the standard under 35 U.S.C. §112, first paragraph, requires the determination of what the claims recite and what the claims mean as a whole. The Examiner further relied on the MPEP, stating that, during patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification (MPEP 2111). However, the Examiner does not correctly apply this standard; the Examiner narrowly interprets the claim scope and requires a vaccine effect even for the claims directed to a method of inducing an immune response. MPEP 2111 stipulates as follows:

> The court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from 'reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.

The Examiner's interpretation is based on the impermissible importation of subject matter from the specification into the claim. Accordingly, a vaccine effect need not be required for claim 20 and its dependent claims, which are directed to a method of inducing an

immune response. Following the MPEP 2111 standard, claim 20 and its dependent claims meet the enablement requirement if these claims are enabling for inducing an immune response.

Moreover, there is no reason to doubt that each of Tat, Rev, Vpu, Vpx, Vpr, Vif, Nef, Gag-Pol fusion protein induces an immune response specific to each virus protein of an immunodeficiency virus in an animal upon intranasal administration. In support of this position, Applicants note the following.

Regarding Tat, an immune response-inducing effect is described in Matano et al. (AIDS 17:1392-1394, 2003), Ensoli et al. (J. Biol. Regul Homeost Agent. 14(1):22-6, 2000), and Cafaro et al. (Nat. Med. 5:643-650, 1999). Van Baalen et al. (Journal of General Virology 78:1913-1918, 1997; copy enclosed) also disclose that Rev- and Tat-specific cytotoxic T lymphocytes (CTL) frequencies inversely correlate with rapid progression to AIDS.

Moreover, Ayyavoo (Vaccine Nov 16(19):1872-9, 1998; previously submitted) discloses induction of an immune response to vif and nef. Ayyavoo (AIDS 14:1-9, Jan 2000; copy enclosed together with copy of the website showing the publication date) discloses that DNA vaccine expressing vif, vpu, and nef induces CTL responses. This DNA vaccine expresses a fusion protein of vif, vpu, and nef with proteolytic cleavage sites, and induces an immune response to each protein (see page 5). In addition, Ayyavoo (AIDS Jan 2000) describes presence of highly conserved T helper and CTL epitopes

within accessory genes (vif, vpu, vpr, and nef) and importance of these genes for vaccine development (see Introduction).

With respect to a part of immunodeficiency virus following administration of a part of an immunodeficiency viral proteins, Applicants direct the Examiner's attention to the following three references which accompany this Reply: Kaur et al., The Journal of Immunology 164: 934-943, 2000; Woodberry et al., Journal of Virology 73(7): 5320-5325, 1999; and Tomiyama et al., Human Immunology 60: 177-186, 1999. These references disclose identification of HIV/SIV-specific CTL epitopes.

For all of the aforementioned reasons, Applicants' specification, coupled with the knowledge of those skilled in the art at the time the application was filed, enables the subject matter encompassed by claim 20 and the rejection should be withdrawn.

Turning to claim 33, Applicants have, to expedite prosecution, amended this claim as follows:

> 33. (currently amended) A method for repressing propagation of an immunodeficiency virus in an animal, the method comprising intranasally administering to said animal a recombinant Sendai virus gene-transfer vector encoding an immunodeficiency viral protein, wherein the immunodeficiency viral protein comprises a protein selected from the group consisting of Gag, Pol, Env, gp41, Tat, ~~Rev, Vpu, Vpx, Vpr, Vif, Nef,~~ and Gag-Pol fusion protein~~, and a part of any of them.~~

Applicants note that the Office has deemed the claimed method enabled for immunodeficiency viral proteins Gag, Pol, gp41, and Gag-Pol. In addition, the Office has acknowledged the vaccine effect of Env, in view of the Hirsch reference relied upon by

the Examiner.

Turning to Tat, the Office asserts that that Allen et al. (J Virol 2002) and the one negative result shown in Matano (AIDS 2003) provide evidence that Applicants' claims are not enabled for the vaccine effect of Tat. Applicants disagree.

In response, Applicants note that Ensoli et al. and Cafaro et al. each disclose the vaccine effect of Tat. Applicants further note that Matano AIDS 2003 discloses two positive results demonstrating the vaccine effect of Tat. Such references provide convincing evidence of enablement of Applicants' specification. Indeed, the weight of the evidence suggests that claim 33 is clearly enabled for Tat. See MPEP 2164.05(a), which states that the determination should always be based on the weight of all the evidence.

The Examiner also asserts that references published after the effective filing date, including Allen et al. (April 2002 and Oct, 2002) and Subbramanian (Sep 2003), cannot be used to support the Applicant arguments (Office Action, page 6). This standard also applies to the Office's examination of this application. MPEP 2164.05(a) states as follows:

> In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977).

Finally, Applicants note that the Examiner, in the current Office Action, relies on

Yu et al. (Curr Medicinal Chemistry 2005;12:741-7) and alleges that "Yu et al. teaches that these accessory proteins are essential for efficient viral replication, but only limited data is available evaluating the role of immune response directed against these proteins in natural HIV-1 infection **and in vaccine development**. (emphasis added)." Applicants have noted that the last phrase "and in vaccine development" cannot be found in thecited passage. Moreover, it is improper to use the Examiner's own interpretation as evidence. Furthermore, the quotation relates to immune response in natural HIV-1 infection. The instant invention relates to artificial induction of immune response and limited data for immune response in natural infection cannot be used as evidence showing non-enablement of the claimed invention. As mentioned above, Applicants submit the references published before the filing date, showing induction of immune response directed to accessory proteins.

For all the above reasons, the 35 U.S.C. § 112, first paragraph rejection of claims 20, 24, 26, 28, 30-33, 37, 39, 41, 43-45, and 63-72 for lack of enablement should be withdrawn.

IV. Rejections under 35 U.S.C. §103(a)

The Office has rejected select claims as obvious under 35 U.S.C. §103 as follows:

(1) Claims 2, 4, 16-19, 65, and 66 stand rejected over Nagai et al. in view of Yu et al. and Hirsch et al.;

(2) Claim 69 was rejected over Nagai et al. in view of Yu et al. and Hirsch et al., and further in view of Hanke et al.;

(3) Claims 2, 4, 5, 7, 9, 16-20, 24, 26, 28-33, 37, 39, 41-45, 62-66, 68-72 stand rejected over Flanagan et al. and Seth et al. in view of Yu et al. and Hurwitz et al, as evidenced by Ourmanov et al., Hanke et al., and Nakanishi et al.;

(4) Claims 11-13 and 15 stand rejected over Flanagan et al. in view of Yu et al. and Kast et al.;

(5) Claim 14 stands rejected over Flanagan et al. in view of Yu et al. and Kast et al., and further in view of Boutillon et al.; and

(6) Claim 67 stands rejected over Flanagan et al. in view of Yu et al. and Kast et al., and further in view of Hanke et al.

Each of these rejections is addressed as follows.

Regarding rejections (1) and (2), Applicants note that Nagai et al., Yu et al., Hirsch et al., and Hanke et al., alone or in combination, fail to render claims 2, 4, 16-19, 65, 66, and 69 obvious.

Nagai et al. and Yu et al. teach the use of Sendai virus as an expression vector. Hirsch et al. discloses the use of vaccinia virus encoding SIV env and gag-pol as an AIDS vaccine. Hanke teaches effective induction of HIV-specific CTL by multi-epitope using gene gun in a combined vaccination regime.

Even if Sendai virus was successfully used to express an immunodeficiency viral

protein, there is no reasonable expectation of success for using Sendai virus in place of vaccinia virus used as a vaccine as taught by Hirsch et al. Vaccinia virus is a DNA virus, whereas Sendai virus is a negative-strand RNA virus. RNA and DNA viruses differ not only in terms of structure but also in terms of functionality and biosynthesis. For example, when a DNA virus infects host cells, a host's cellular enzymes transcribe viral DNA to make mRNA and the host cell translation machinery translates the mRNA into protein. In contrast, when Sendai virus infects host cells, Sendai viral genomic RNA (negative strand RNA) is transcribed into antigenomic RNA by the viral RNA-dependent RNA polymerase, the antigenomic RNA is used to replicate the genomic RNA, copied genomic RNA is transcribed into mRNA which is translated into protein. In view of such very different replication systems between DNA virus and negative-strand RNA virus, one skilled in the art would not have reasonable expectation of success for use of negative-strand RNA virus expressing an immunodeficiency viral protein as a vaccine or a vector that can induce an immune response to the immunodeficiency viral protein, even if DNA virus is known to be used as a gene-transfer vector for vaccination and negative-strand RNA virus is known to be used as an expression vector.

The secondary reference Hanke neither suggests nor motivates the skilled worker to arrive at the claimed invention.

Accordingly, the 2, 4, 16-19, 65, 66, and 69 are not obvious over the cited references, and rejections (1) and (2) should be withdrawn.

Turning to rejections (3) to (6), Flanagan et al. and Yu et al. are commonly cited. For the following reasons, the combined teachings of these references fail to make a *prima facie* case for obviousness, and the rejections should be withdrawn.

Flanagan et al. teaches using a recombinant adenovirus expressing SIV Gag protein for vaccination. Adenovirus, as well as vaccinia virus taught in Hirsch et al., is a DNA virus. As discussed above, RNA and DNA viruses differ in replication and protein expression systems. Therefore, even if adenovirus expressing an immunodeficiency viral protein is known to be used as a vaccine that induces an immune response to the immunodeficiency protein and Sendai virus is known to express an immunodeficiency viral protein as an expression vector, one skilled in the art would not have a reasonable expectation of success for using Sendai virus expressing an immunodeficiency viral protein for induction of an immune response specific to the immunodeficiency viral protein.

For this reason alone, rejections (3) to (6) should be withdrawn.

In addition, Applicants address several issues raised by the Office in connection with the Nakanishi et al., Yu et al., Hurwitz et al., and Hasan et al. references.

In connection with Applicants' amendment reciting "Sendai virus gene-transfer vector," the Office asserts that the specification "fails to make a distinction for the structural differences between [a sendai virus] "expression vector" and "gene transfer vector" [Office Action, page 13]." The Office also alleges that in view of the state of the

art at the time of the priority date, gene transfer by a viral vector is closely associated and measured by the levels of transgene expression, and there is no clear distinction between a gene transfer vector and an expression vector. To support this assertion, the Office relies on Nakanishi et al. for the proposition that "we must deliver genes efficiently in situ and induce stable gene expression in non-dividing cells". Applicants disagree.

In this instance, the Office has not considered all the limitations of the claims. In particular, the Office has not considered the phrase "gene-transfer." Such an analysis is improper. According to MPEP 2143.03, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art and *all words in a claim must be considered in judging the patentability of that claim against the prior art.* Furthermore, the sentence quoted from Nakanishi et al. does not describe that gene transfer is practiced with an expression vector. Rather, Nakanishi et al. teach that current viral vectors are not considered to be ideal tools for human gene therapy, and the authors developed fusogenic liposome generated by fusion of a liposome and a Sendai virus particle in which viral genome has been inactivated (see pages 62-63). Such fusogenic liposomes cannot be used as an expression vector. For this reason too, Nakanishi et al. cannot support the Examiner's position. The teachings of Nakanishi et al., which disclose defects of viral vectors, would not have motivated one skilled in the art to use Sendai virus itself as a gene-transfer vector.

Regarding Yu et al., the Office asserts that Yu et al. stressed the usefulness of the

vector in expressing a transgene in a wide variety of mammalian cells, and compared the Sendai viral vector with the gene transfer vector taught by Seth et al., which indicates that Yu et al. is fully aware the use of V(-) Sendai virus vector for gene transfer. Applicants again disagree with the Office.

As noted previously, Yu et al. compares Sendai virus with vaccinia virus in terms of the expression level as an expression vector. The fact that Yu et al. compared the two viruses does not mean that Yu et al. was aware the use of V(-) Sendai virus vector for gene transfer. Such is a mere speculation by the Examiner. Nowhere in Yu et al. is there a suggestion that vaccinia virus is used as a gene-transfer vector. It is also noted that Yu et al. was published in 1997 and Seth et al. was published in 1998. Yu et al. therefore could not have been aware the disclosure of Seth et al.

Furthermore, the fact that the expression level from Sendai virus is comparable to the vaccinia virus-based expression would not provide a reasonable expectation of success for using Sendai virus as a gene-transfer vector. As discussed above, vaccinia virus and Sendai virus differ in replication and protein expression systems. When used as a gene-transfer vector, one skilled in the art would not have readily predicted that Sendai virus encoding an immunodeficiency viral protein can serve as a vaccine or can be used to induce an immune response specific to the immunodeficiency viral protein.

Furthermore, the Office contends that Hurwitz et al. was cited to show the desirability and the feasibility of intranasal multiple inoculation of a Sendai virus in

primates. Indeed, Hurwitz et al. teaches that wild-type Sendai virus could survive in the nasal cavity of primates for several days. However, it would not have been obvious as to whether a recombinant Sendai virus expressing an exogenous gene persists in the nasal cavity for several days as found for wild-type virus. Hasan et al. discloses that the increase in genome length was associated with slightly slower replication kinetics and a severalfold decrease in yield of the virus (see Abstract). From such teachings, one skilled in the art would not have a reasonable expectation of success for using a recombinant Sendai virus vector to achieve replication and protein expression in primate's nasal cavity similar to wild-type Sendai virus.

The Examiner also asserts that "Yu et al. cited Hasan et al reference and indicated the aggregation of the luciferase made it difficult to measure the amount of protein production, which is not to say the product is not functional." Further, the Examiner argued that Hasan et al. teaches measuring the luciferase enzyme activity. The Office seems to miss the point. As the Examiner has noted, Applicants argued that it is questionable whether a Sendai virus vector encoding a foreign gene could produce a foreign gene product that is functional *to induce an immune response specific to the product.* Thus, the function to be questioned is not protein activity, but the function to induce an immune response. Hasan et al. does not disclose whether aggregated luciferase protein is antigenically authentic.

V. Double Patenting

Claims 2, 4, 16-19, 65, 66, and 69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 5, and 13 of U.S. Patent 7,101,685, in view of Yu et al., Hirsch et al., and Hanke et al.

Applicants submit that, for the reasons presented above in connection with the rejections (1) and (2), claims 2, 4, 16-19, 65, 66, and 69 are non-obvious over claims 1, 4, 5, and 13 of U.S. Patent 7,101,685. The obviousness-type double patenting rejection should therefore be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including March 14, 2007, and a check for payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 14 March 2007

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